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Homotopic connectivity in drug-naïve, first-episode, early-onset schizophrenia

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Background: The disconnection hypothesis of schizophrenia has been extensively tested in adults. Recent studies have reported the presence of brain disconnection in younger patients, adding evidence to support the neurodevelopmental hypothesis of schizophrenia. Because of drug confounds in chronic and medicated patients, it has been extremely challenging for researchers to directly investigate abnormalities in the development of connectivity and their role in the pathophysiology of schizophrenia. The present study aimed to examine functional homotopy – a measure of interhemispheric connection – and its relevance to clinical symptoms in first-episode drug-naïve early-onset schizophrenia (EOS) patients. **Methods:** Resting-state functional magnetic resonance imaging was performed in 26 first-episode drug-naïve EOS patients (age: 14.5 ± 1.94, 13 males) and 25 matched typically developing controls (TDCs) (age: 14.4 ± 2.97, 13 males). We were mainly concerned with the functional connectivity between any pair of symmetric interhemispheric voxels (i.e., functional homotopy) measured by voxel-mirrored homotopic connectivity (VMHC). **Results:** Early-onset schizophrenia patients exhibited both global and regional VMHC reductions in comparison with TDCs. Reduced VMHC values were observed within the superior temporal cortex and postcentral gyrus. These interhemispheric synchronization deficits were negatively correlated with negative symptom of the Positive and Negative Syndrome Scale. Moreover, regions of interest analyses based on left and right clusters of temporal cortex and postcentral gyrus revealed abnormal heterotopic connectivity in EOS patients. **Conclusions:** Our findings provide novel neurodevelopmental evidence for the disconnection hypothesis of schizophrenia and suggest that these alterations occur early in the course of the disease and are independent of medication status. **Keywords:** Resting-state fMRI, early-onset schizophrenia, functional connectivity, interhemispheric connectivity.

Introduction

Schizophrenia is a severe psychotic disorder that affects approximately 1% of the population (Lopez & Murray, 1998) and is increasingly considered a disconnection syndrome (Friston & Frith, 1995; Frith et al., 1995; Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011). Using a recently developed brain imaging technique, resting-state functional magnetic resonance imaging (RFMRI), a large number of studies have shown that patients with schizophrenia exhibit deficits in functional connectivity (Fornito, Zalesky, Pantelis, & Bullmore, 2012; Schmitt, Hasan, Gruber, & Falkai, 2011; Stephan, Baldeweg, & Friston, 2006). Pettersson-Yeo et al. (2011) systematically reviewed the RFMRI literature on schizophrenia and found that most studies consistently report decreased functional connectivity in different stages of schizophrenia (high-risk, early-onset, first-episode, chronic). This decreased connectivity appeared mainly between the frontal lobe, the fronto-temporal lobe, the corpus callosum, the anterior cingulate gyrus and other cortical and subcortical brain regions (Pettersson-Yeo et al., 2011). Of note, most of the studies in the review focused on adulthood-onset schizophrenia, with only a few studies investigating functional connectivity in early-onset schizophrenia (EOS) patients.

'Early onset' refers to an onset of psychosis before the 18th birthday (Rhinewine et al., 2005; Vourdas, Pipe, Corrigall, & Frangou, 2003). Early-onset patients have been found to be more impaired and have poorer outcomes than adult-onset schizophrenia patients (Rhinewine et al., 2005; White, Schmidt, Kim, & Calhoun, 2011). The neurodevelopmental hypothesis of schizophrenia proposes that abnormal neurodevelopment causes the illness (Owen, O'Donovan, Thapar, & Craddock, 2011; Rapoport, Giedd, & Gogtay, 2012; Weinberger, 1987). This highlights the importance of investigating the neurodevelopment of EOS, especially first-episode drug-naïve patients. Until now, few studies have explored functional connectivity using RFMRI in EOS patients. Ke et al.(2009) first observed reduced functional connectivity between right frontal regions and other brain regions in EOS patients. EOS patients also exhibited decreased functional connectivity between the cingulate gyrus and a variety of areas including frontal, temporal, occipital, and subcortical regions (Zhou, Tan, Tang, & Chen, 2010). Alexander-Bloch and colleagues reported that childhood-onset schizophrenia (COS, defined as

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onset before age 13 years) patients showed deficits in whole-brain network local organization and brain modular community structure (Alexander-Bloch et al., 2010, 2012, 2013). Of note, in these studies, most of the EOS and COS patients were medicated. These studies therefore involve a potential confounding effect of medication on the differences in functional connectivity. Antipsychotic medication has been shown to influence functional brain connectivity in schizophrenia (Honey et al., 1999).

Increasing evidence suggests that the disconnection syndrome in schizophrenia might include disruption of interhemispheric connectivity, as found in previous behavioral (Barnett, Kirk, & Corballis, 2007; Mohr, Pulvermuller, Cohen, & Rockstroh, 2000) and psychophysiological studies (Mohr, Pulvermuller, Rockstroh, & Endrass,2008; Morrison-Stewart, Velikonja, Corning, & Williamson, 1996). Much of this interaction is mediated by the corpus callosum, which primarily connects homotopic regions of the two hemispheres (Hoptman & Davidson, 1994). As a fundamental characteristic of intrinsic brain architecture (Stark et al., 2008), functional homotopy – voxel-mirrored homotopic connectivity (VMHC) undergoes remarkable dynamic changes during the life span (Zuo et al., 2010). Using the VMHC approach, two studies reported reductions in functional homotopy in adult schizophrenia (Guo et al., 2014c; Hoptman et al., 2012).

Up to now, few studies investigated the functional connectivity in EOS, and no studies explored the functional connectivity in unmedicated EOS patients. This highlights the need for investigations focused on brain connectivity in drug-naïve EOS patients. In the present study, we examined neuroimaging data from 26 drug-naïve first-episode EOS patients and 25 demographically matched typically developing controls (TDCs). We used the VMHC method to examine potentially abnormal functional homotopy in this early stage of schizophrenia.

Materials and methods

Participants

Thirty-two EOS patients were recruited from the first hospital of Shanxi Medical University. The clinical diagnosis was made by two consultant psychiatrists according to a Chinese version of the Modified Structured Clinical Interview for DSM-IV for patient version (SCID-I/P). The patients who have other Axis-I or Axis-II comorbidity disorders were excluded. The age of the EOS patients ranged from 9.0 to 17.9 years. All patients were in their first episode and were drug-naïve when they received the neuroimaging scanning. Clinical symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). These patients had no history of other major psychiatric illness, neurological illness, head injury, alcohol or drug abuse.

Thirty TDCs were recruited from advertisements posted in the community and by word of mouth. They were interviewed with the Structured Clinical Interview for DSM-IV for nonpatient version (SCID-I/NP) and were selected to match members of the EOS group for gender and age. The age of the healthy controls ranged from 7.5 to 17.5 years. None of TDCs had any significant prior medical diagnosis, substance abuse, neurological disorders, or major psychiatric disorders. Those who had a first-degree relative with a history of severe mental disorder or suicidal behavior were also excluded.

Written informed consent was obtained from each participant and consent from each participant's guardian was also obtained prior to data acquisition. This study was approved by the Ethical Committee for Medicine of First Hospital of Shanxi Medical University, China.

MRI acquisition

Magnetic resonance imaging scanning was performed on the 3.0T Siemens Trio™ Scanner (Erlangen, Germany) at the First Hospital of Shanxi Medical University. For each participant, both an 8-min and 52-s RFMRI scan with echo planar imaging sequence (EPI: TR = 2,500 ms, TE = 30 ms, flip angle = 90°, matrix = 64 × 64, FOV = 240 mm, 4 mm slice thickness, 32 axial slices, 212 acquisitions) and a T1-weighted structural MRI scan with magnetization-prepared rapidly acquired gradient echo sequence (MPRAGE: TR = 2300 ms, TE = 2.95 ms, TI = 900 ms, flip angle = 9°, matrix = 240 × 256, FOV = 225 × 240 mm, slice thickness = 1.2 mm, 160 slices) were acquired. For the resting-state scan, participants were instructed to close their eyes and remain awake while lying quietly.

Data analysis

Image preprocessing was conducted with the Connectome Computation System (CCS: http://lfcd.psych.ac.cn/ccs.html), including both structural and functional image preprocessing (Zuo et al., 2013). Briefly, the functional scans were slice-timing corrected, motion corrected, normalized with a 4D mean of 10,000, filtered with a temporal band-pass filter (0.01–0.1 Hz) and finally registered with individual anatomical images and further with the standard symmetric template. Data quality control procedure (QCP) was conducted to ensure usable data for subsequent analyses. For each participant, VMHC was computed as the resting-state functional connectivity (RSFC) between every pair of symmetric interhemispheric voxels (Zuo et al., 2010). Online supplementary Appendix S1 provides further details about the data analysis, such as the VMHC computation and generation of the standard symmetric brain template.

Group-level analyses were conducted using FSL's ordinary least squares (OLS) model implemented in FLAME. Voxel-wise one-way ANCOVA tests (covariates: age, sex, the error of nonlinear registration, minimal cost of coregistration, root mean square of frame-wise displacement, global VMHC (gVMHC), voxel-mirrored homotopic morphometry (VMHM) of the gray matter density) were performed to examine the differences in regional VMHC between the two groups. This statistical procedure produced thresholded Z-statistic maps of clusters defined by a threshold of $Z = 2.3$ and a cluster-level threshold based on Gaussian Random Field theory with a cluster-level family-wise error (FWE) correction for multiple comparisons (corrected $p < .05$). Of note, the gVMHC was also evaluated with a similar ANCOVA model (but without the covariates of gVMHC and VMHM) to test group differences.

Results

Demographic and clinical characteristics

Demographic and clinical information is listed in Table 1. Two EOS patients did not complete the scanning, and four other patients' data did not pass

Table 1 Participant information

	EOS ($N = 26$)	TDC ($N = 25$)
Age	14.5 (1.94)	14.4 (2.97)
Sex (male/female)	13/13	13/12
gVMHC*	0.2165 (0.0447)	0.2418 (0.0401)
errFNIRT[a]	0.0873 (0.0164)	0.0824 (0.0109)
mcBBR[b]**	0.5111 (0.0436)	0.5443 (0.0356)
rmsFD[c](mm)	0.1147 (0.0562)	0.1121 (0.0477)
Total PANSS score	57.75 (13.74)	–
Positive symptoms	12.04 (3.94)	–
Negative symptoms	13.17 (4.93)	–
General psychopathology	28.58 (6.89)	–
Supplementary items	3.96 (1.57)	–

The values in brackets are standard deviations. EOS, Early-Onset Schizophrenia; TDC, Typical Development Control; VMHC, voxel-mirrored homotopic connectivity. Positive and Negative Syndrome Scale (PANSS) scores were available for 24 EOS patients.
[a]errFNIRT is the registration error of the individual spatial normalization to the MNI152 standard space (2 mm isotropic voxels) measured by 1 – the spatial correlation between individual normalized T1 images and the standard template.
[b]mcBBR is the minimal cost of the intrasubject coregistration with the boundary-based registration.
[c]rmsFD is the root mean square of the frame-wise displacement for in-scanner head motion.
*$p < .05$; **$p < .01$.

the imaging data QCP. Data from five TDCs were excluded for failure to pass the QCP. The final sample included 26 EOS patients and 25 TDCs.

Functional homotopy in TDCs and EOS

The spatial patterns of VMHC across the whole brain are shown in Figure 1 for TDCs (Figure 1A) and EOS patients (Figure 1B). Both groups exhibited the greatest VMHC in the precuneus and posterior cingulate cortex (PCU/PCC), followed by the insula, precentral gyrus (PRG), postcentral gyrus (PCG), superior temporal cortex (STC), and middle occipital gyrus, as well as subcortical areas. The lateral prefrontal cortex showed relatively weaker VMHC in both groups. On visual inspection, although the two groups showed similar patterns in VMHC, TDCs seemed to have stronger VMHC in PCU, PCG, STC, and occipital cortex.

Group differences in functional homotopy

To assess structural confounders to the VMHC, we investigated the gray matter density and cortical thickness differences between EOS patients and TDCs. No significant differences were detectable in these two metrics between the two groups. Moreover, the data preprocessing was performed with two approaches, with scrubbing and without scrubbing. The results were reproducible across these two approaches, and here we only present the results without scrubbing in following sections.

Early-onset schizophrenia patients showed significantly reduced gVMHC in comparison with TDCs, indicating a deficit of whole-brain interhemispheric synchronization in EOS patients (Table 1). As seen in Figure 2A, EOS patients exhibited significantly lower VMHC in a cluster overlapping the STC/PCG. We also compared VMHC in the 24 EOS patients who had PANSS scores and the TDCs, and observed a similar decrease of VMHC in EOS patients (Figure 2B).

To evaluate the effects of disrupted interhemispheric connectivity on the relevant resting-state networks, we used clusters of left and right STC/PCG as two regions of interest (including all voxels in the clusters of the left or right STC/PCG) to

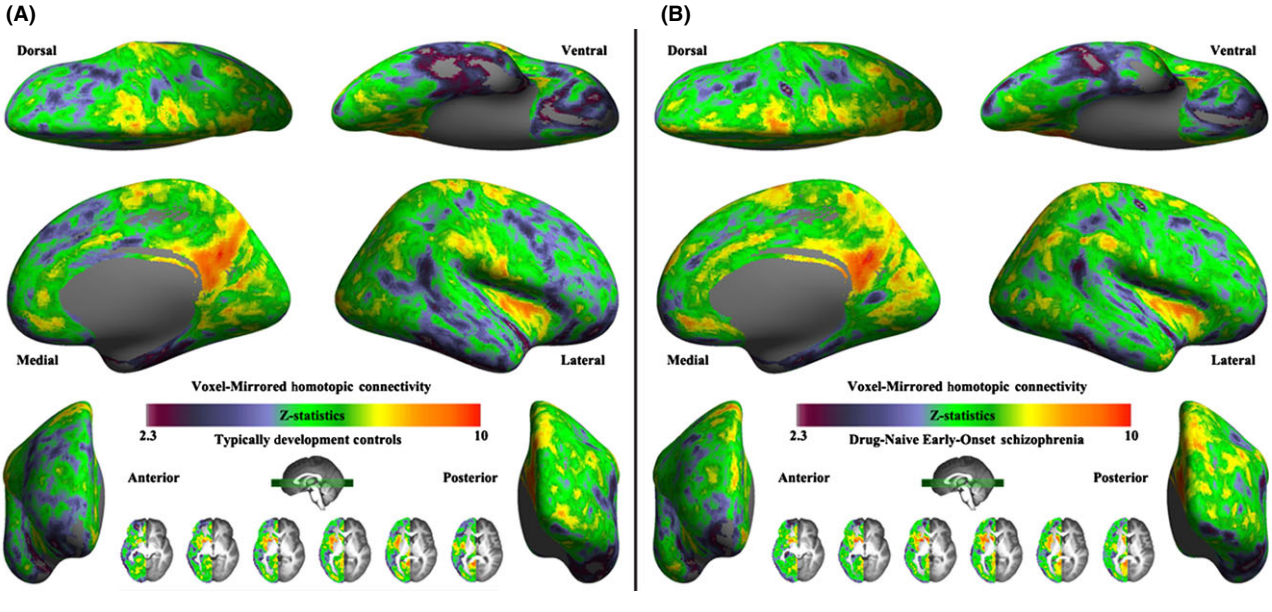

Figure 1 Whole-brain voxel-wise homotopic functional connectivity patterns in early-onset schizophrenia (EOS) patients (A) and typically developing controls (TDCs) (B)

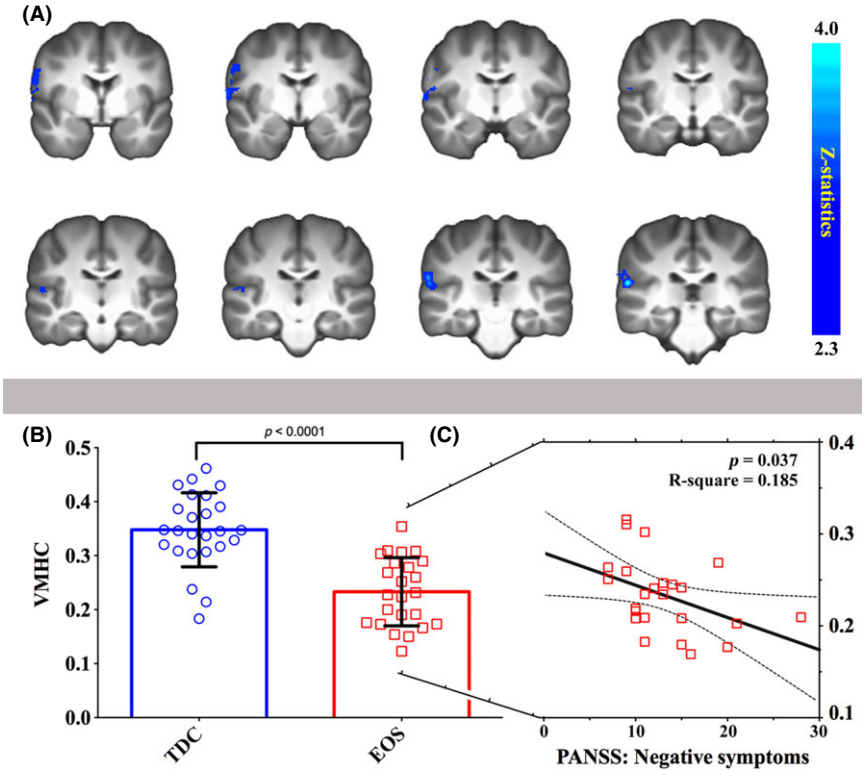

Figure 2 (A) Comparisons of whole-brain voxel-mirrored homotopic connectivity (VMHC) between early-onset schizophrenia (EOS) patients and typically developing controls (TDCs). The cool colors indicate regions showing higher VMHC in TDCs than EOS patients. (B) Comparisons of whole-brain VMHC in the 24 EOS patients who had Positive and Negative Syndrome Scale scores and the TDCs. Each VMHC value here came from the cluster in A. (C) Correlation between the mean VMHC of the superior temporal cortex/postcentral gyrus and negative symptoms in EOS patients

investigate the patterns of intrinsic functional connectivity (iFC) with the whole brain in both EOS and TDC groups, as well as group differences in iFC. The clusters of the left and right STC/PCG were defined as the cluster showing the VMHC group differences between EOS patients and TDCs and its left–right flipped version. We found that in TDC participants, the left STC/PCG showed positive iFC with the precentral and postcentral gyri, supplemental motor area, superior and middle temporal gyri, middle frontal gyrus, anterior cingulate cortex, and anterior cerebellum. The left STC/PCG was negatively connected with the frontal pole, PCC, PCU, lateral occipital cortex, superior frontal gyrus, and medial frontal gyrus (Figure 3A: the left column). The right STC/PCG exhibited similar iFC patterns (Figure 3A: the right column). The iFC patterns seeded in the bilateral STC/PCG in the EOS group (Figure 3B) were highly similar but weaker in strength than those for TDC group. The group comparisons of left STC/PCG iFC analysis revealed that the EOS patients showed iFC reductions in the bilateral PCG, PRG, supplemental motor area, STC, and insula, as well as increased iFC in the bilateral caudate, medial prefrontal gyrus, thalamus, PCC, and PCU when compared with TDCs (Figure 4A). The right STC/PCG iFC analysis showed highly similar findings with the left STC/PCG iFC results (Figure 4B).

Correlations with clinical scores in early-onset schizophrenia patients

Mean VMHC of the STC/PCG was negatively correlated with negative symptoms ($r = -.43$, $p = .037$) (Figure 2C) and marginally correlated with total PANSS score ($r = -.36$, $p = .085$). No significant correlations were found between the gVMHC and PANSS total and subscale scores or the mean VMHC within the STC/PCG and other subscale scores. To gain insights into the item-specific contribution to these correlations, we further examined the correlation between the VMHC and each item score in PANSS and detailed the findings in Appendix S1. Correlational analyses of iFC findings and the PANSS items can also be found in Appendix S1.

Reproducibility

To examine the reproducibility of our findings reported, we performed both the split-half and leave-one-out validations. First, 13 EOS patients and 13 TDCs were randomly selected from the sample and entered into the same statistical comparisons. The findings were depicted as in Figure 5A and fundamentally replicated the findings from the full sample. Notably, the sample size was relatively small and the split-half analysis may significantly reduce the statistical power of the group

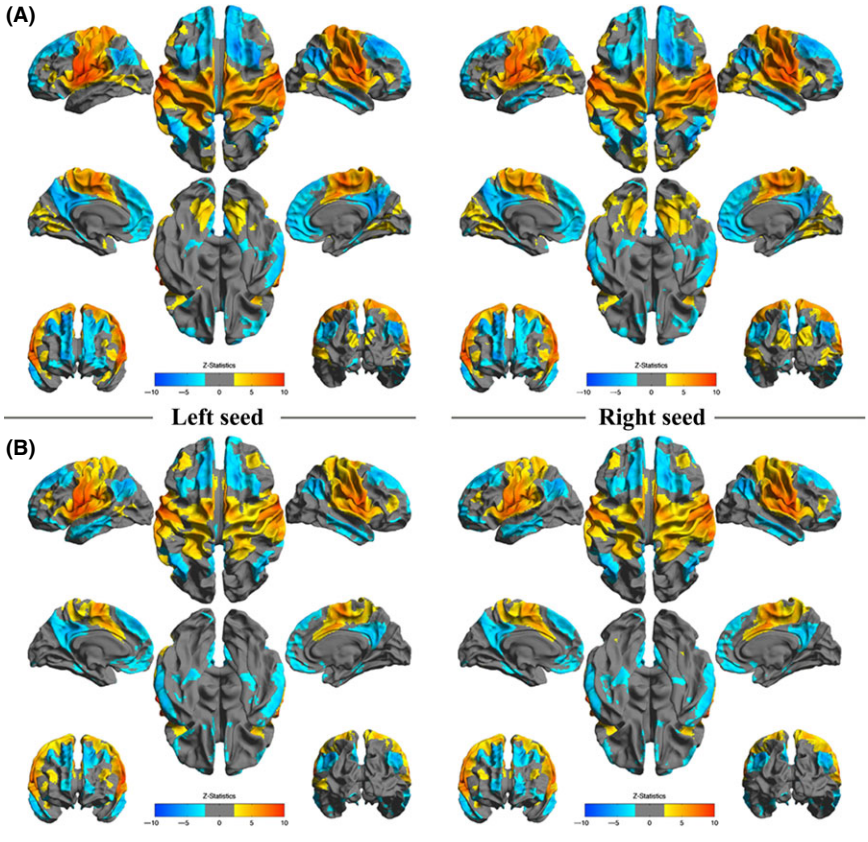

Figure 3 Intrinsic functional connectivity patterns for left and right superior temporal cortex (STC)/postcentral gyrus (PCG) seeds: (A) early-onset schizophrenia (EOS) patients; (B) typically developing controls (TDCs). The figure is presented in neurological convention (image left is the left side of the brain). The left and right panels corresponded to the left and right STC/PCG seeds, respectively

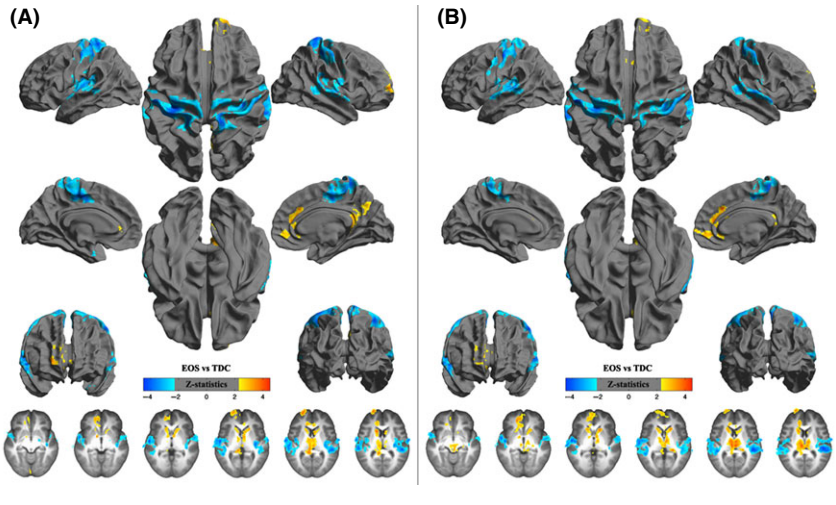

Figure 4 Group differences in intrinsic functional connectivity between early-onset schizophrenia (EOS) patients and typically developing controls (TDCs): (A) left superior temporal cortex (STC)/postcentral gyrus (PCG) seed; (B) right STC/PCG seed

comparisons. This limitation is reflected by the following seed-based iFC analysis in the other half of the sample. The overall previous findings of iFC (Figure 4) were largely limited to the spatial extent of the half sample (Figure 6).

To validate the reproducibility and robustness of these findings on VMHC without losing statistical power, we performed a leave-one-out validation. Specifically, we left one EOS patient out of the sample and performed the same group comparisons based upon the permutated sample (i.e., 25 EOS vs. 25 TDC). This analysis led to total 26 two-sample *t*-test images, based on which, for each voxel, we calculated number of tests where this voxel exhibited significant group differences across the total 26 tests as the reproducibility of the VMHC differences between EOS patients and TDC. Figure 5B indicated highly reproducible patterns of VMHC reductions across these tests as well as the original test reported.

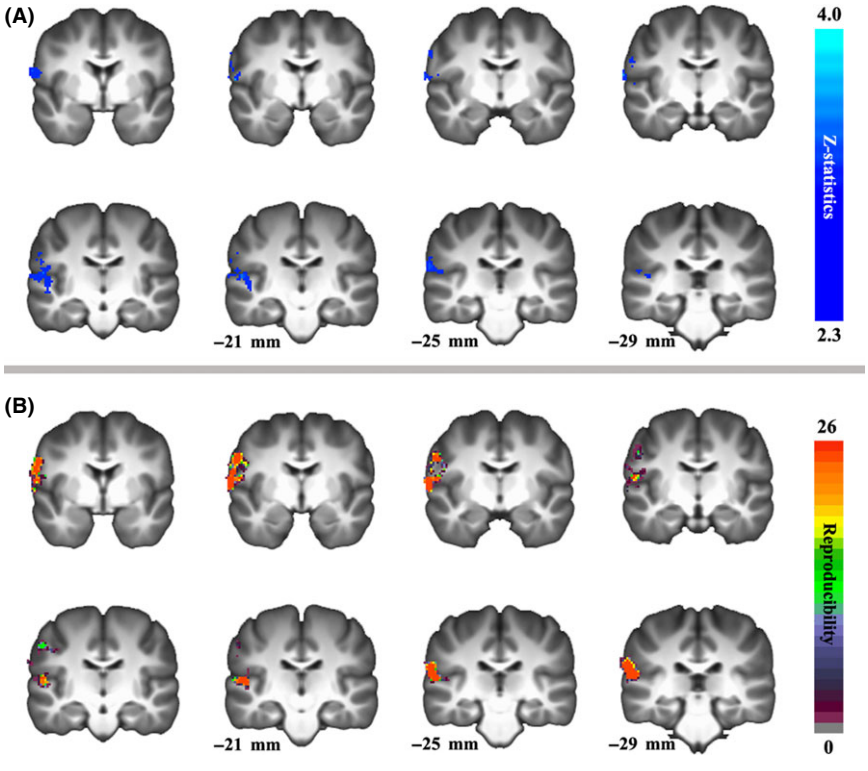

Figure 5 (A) Split-half sample validation. Comparisons of whole-brain voxel-mirrored homotopic connectivity (VMHC) were performed between 13 early-onset schizophrenia (EOS) patients and 13 typically developing controls (TDCs). The cool colors indicate regions showing higher VMHC in TDCs than EOS patients. (B) Leave-one-out sample validation. The group comparisons based upon the permutated samples (i.e., 25 EOS vs. 25 TDC) for total 26 times. For each voxel, the color indicates number of tests where this voxel exhibited significant group differences across the total 26 tests (i.e., the reproducibility)

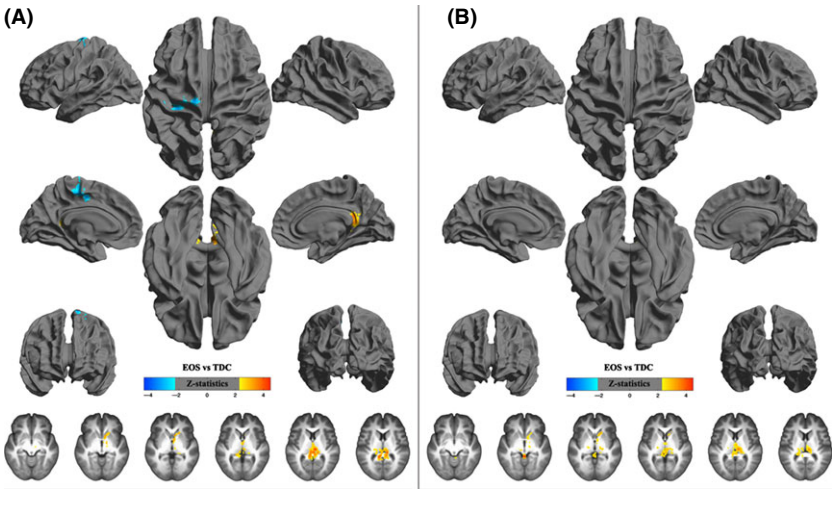

Figure 6 Split-half validation derived group differences in intrinsic functional connectivity between 13 early-onset schizophrenia (EOS) patients and 12 typically developing controls (TDCs): (A) left superior temporal cortex (STC)/postcentral gyrus (PCG) seed; (B) right STC/PCG seed

Discussion

The current observation that drug-naive EOS patients show substantial deficits in interhemispheric coordination provides neurodevelopmental evidence for the disconnection hypothesis of schizophrenia. Thus, alterations in functional homotopy in EOS patients might occur early on in the course of the illness and be independent of medication status.

Early-onset schizophrenia patients exhibited reduction of global whole-brain interhemispheric low-frequency synchronization in comparison with TDCs. The present findings are consistent with recent studies reporting that COS patients exhibited a disrupted functional organization in their brain connectomes. Using a graph theory approach, Alexander-Bloch and colleagues observed reduced modularity and local organization in brain functional networks in

chronic and medicated COS patients (Alexander-Bloch et al., 2010, 2012). Guo et al. (2013) investigated the brain-wide functional interhemispheric connections in adult schizophrenia, and found reduced brain-wide interhemispheric functional networks. Our work employed drug-naïve first-onset EOS patients and provides strong evidence that these disruptions in the global metrics of whole-brain functional connectomes might be an indication of the reduction of global hemispheric communication occurring in patients during development.

The regionally specific reduction of VMHC in the EOS group was mainly detected in the STC and extended to the PCG. With the same approach, Guo et al. (2014c) found that first-episode, drug-naïve paranoid schizophrenia patients showed decreased VMHC in STC. The STC is considered to be responsible for auditory and language processing (Bigler et al., 2007; Menon et al., 1995). These results are consistent with well-established deficits shown by patients with schizophrenia in auditory processing (Javitt, 2009). Previous studies have reported that this region has abnormal features of both gray matter and white matter in COS and EOS patients (Tang et al., 2012; Taylor et al., 2005). Meanwhile, task-based fMRI studies have reported that adult schizophrenia patients show decreases in STC activation during language processing (Kircher, Leube, Erb, Grodd, & Rapp, 2007; Simons et al., 2010), the auditory oddball task (Kiehl & Liddle, 2001), and verbal working memory (Pae et al., 2008) compared with healthy controls. Additionally, EOS patients showed decreased activation in the STC during encoding stage of working memory (Haenschel et al., 2007). Another study found that the encoding-related bilateral anterior cingulate and temporal lobe network were disrupted in EOS patients during a working memory task (White et al., 2011). Moreover, adult schizophrenia patients also showed reduced interhemispheric EEG coherence in the temporal lobe (Winterer et al., 2001). The PCG is considered to be a key structure for receiving and processing somatosensory information (Nelson & Chen, 2008; Taylor & Jones, 1997). The decreased VMHC in this region suggests that EOS patients may have deficits in primary somatosensory processing.

The seed-based analysis revealed abnormal non-homotopic connectivity in EOS patients. The strength of functional connectivity of the STC/PCG in the EOS group was weaker than in the TDC group for both negative and positive iFC. More interestingly, EOS patients showed similar abnormal iFC patterns for left and right seeds of the STC/PCG, suggesting that the lower VMHC in EOS patients contributed to the dysfunctions in both hemispheres, as has been found in adult patients (Hoptman et al., 2012). In comparison to TDCs, EOS patients showed decreased iFC in bilateral PCG and STC; these findings were consistent with the VMHC group comparisons. EOS patients also showed decreased iFC in supplemental motor area and insula in comparison with TDCs. Insula is considered to play an important role in various aspects of emotional and cognitive processing (Augustine, 1996), while supplemental motor area is involved in internal movement generation and movement sequence construction (Goldberg, 1985; Tanji, 1994). These results suggested that EOS patients might also show abnormalities in emotion, cognition, and movement processing. Increased iFC was found in medial prefrontal gyrus, PCC, and PCU in EOS patients, these regions located in the default mode network. The present results were consistent with previous findings in adult schizophrenia (Garrity et al., 2007), possibly representing the boundary between imagination and reality (Buckner, Andrews-Hanna, & Schacter, 2008) is disrupted in early stage of the schizophrenia. The thalamus plays an important role in relaying and receiving the sensory and motor signals (Crick, 1984), while caudate nucleus is involved in the learning and memory (Grahn, Parkinson, & Owen, 2008). Increased iFC between the STC/PCG and regions responsible for sensory and goal-directed processing might represent decreased functional segregation in EOS patients (Fair et al., 2009). Moreover, nonhomotopic functional connectivity disruptions have also been found in adult schizophrenia (Fornito et al., 2012; Schmitt et al., 2011; Stephan et al., 2006) and COS patients (Alexander-Bloch et al., 2010, 2012, 2013). Disrupted homotopic as well as nonhomotopic connectivity in EOS patients suggested that the disconnectivity might be the more general symptom of schizophrenia.

To the best of our knowledge, the present work represents the first study to investigate functional connectivity with unmedicated EOS patients. Consistent with our previous work on adult chronic schizophrenia patients (Hoptman et al., 2012), only decreased functional homotopy was detected in EOS patients, although the regions showing decreased connectivity were different between the two studies, suggesting medication and/or age effects. Guo et al. (2014a) revealed that healthy controls had more long-range interhemispheric connections than patients with schizophrenia (62% vs. 52%). However, they found that patients with schizophrenia showed increased mean connectivity strength for both short- and long-range interhemispheric links. This study used the automated anatomical labeling (AAL) atlas to parcellate the brain into 90 regions of interest (45 for each hemisphere), whereas VMHC approach was adopted in our study. Moreover, in the study of Guo et al. (2014a), adult patients with schizophrenia were recruited, and three quarters of the patients were receiving antipsychotic medications. The potential effects of antipsychotic drugs on brain structure in psychosis are receiving increasing attention. Navari and Dazzan (2009) systematically reviewed 33 studies investigating the association of antipsychotic medication and brain structure changes and

concluded that the influences of antipsychotic treatment on the brain changes in psychosis are mostly regional and not global. In particular, antipsychotic treatment has been associated with reduced gray matter volume in the frontal and temporal lobes (Smieskova et al., 2009). Even short-term (mean 8.5 weeks) antipsychotic treatment might cause gray matter reduction in frontal and temporal-insular areas and the precuneus (Dazzan et al., 2005), and long-term antipsychotic treatment with different doses or types of antipsychotics presents further challenges to the interpretation of brain changes. Importantly, antipsychotic medications have also been found to affect brain activity or functional connectivity in schizophrenia. Researchers explicitly tested the effect of antipsychotics on brain function in drug-naïve adult schizophrenia before and after 6 weeks of treatment and observed increased regional amplitudes of intrinsic brain activity of the bilateral prefrontal, parietal, left superior temporal cortex and right caudate nucleus, as well as widespread decreased functional connectivity in schizophrenia patients (Lui et al., 2010). A recent study employing healthy volunteers also provided evidence that antipsychotic medications might attenuate the functional connectivity patterns (Cole et al., 2013). The results we report here in drug-naïve EOS patients exclude the effects of antipsychotics and suggest abnormal interhemispheric functional coordination in schizophrenia, even in unmedicated patients.

Several possible mechanisms may underlie the reductions of VMHC in EOS patients. Altered brain structures might disrupt the functional synchrony between homotopic regions. The splenium of the corpus callosum connects left and right parietal and temporal areas (Hofer & Frahm, 2006; Knyazeva, 2013). A recent study reported that first-episode drug-naïve adult schizophrenia patients showed reduced FA in the splenium, but not the genu, of the corpus callosum (Gasparotti et al., 2009). Because the fiber tracts in the splenium of the corpus callosum interconnect temporal cortical areas, an altered corpus callosum structure may disrupt the neural signal transmitted from one hemisphere to another, leading to failure of functional integration or disrupted VMHC in EOS patients. A recent study found that long-range connections increased, whereas local connections decreased in adolescence (Dosenbach et al., 2010). We found decreased VMHC in EOS patients in a specific type of long-range connection, interhemispheric connectivity, implying that these decreases might reflect disruptions in functional integration during development. The disruptions of functional integration are associated with myelination, axon terminal arborization, and synapse formation (Fair et al., 2007, 2009). Another possible factor underlying abnormal functional homotopy is asymmetry of hemispheric growth in EOS patients. The two hemispheres may show subtle differences or delays in the trajectory of growth in schizophrenia (Bleich-Cohen, Hendler, Kotler, & Strous, 2009; Crow, 1998), as was found in the present seed-based analyses.

Specifically, previous studies have demonstrated disrupted functional connectivity in siblings of schizophrenia patients. Patients with schizophrenia and their unaffected siblings were found to show impaired brain connectivity between brain networks as well as within networks (Repovs, Csernansky, & Barch, 2011). Chang et al. (2014) reported that patients with schizophrenia and their siblings shared disconnection within the anterior DMN, as well as in the left and right fronto-parietal network subsystems. Increased functional connectivity between the bilateral inferior temporal gyri was also found in patients with schizophrenia and their unaffected siblings (Liu et al., 2012). With the same VMHC approach, Guo et al. (2014b) found that siblings of schizophrenia patients (mean age = 22.96 years old) showed lower VMHC in angular gyrus, lingual gyrus/cerebellum lobule VI than healthy controls. These results found in unaffected siblings suggest that the disconnection may precede the psychosis and represent a vulnerability toward the illness. Most previous studies focused on the adult schizophrenia patients and their adult siblings, and few studies investigated the functional connectivity in EOS patients and their adolescent siblings. Future studies about EOS patients and their adolescent siblings would provide further neurodevelopmental evidence for the disconnection theory of schizophrenia.

The findings further extend the association between clinical symptoms and functional connectivity in EOS patients. The mean VMHC of the STC/PCG was correlated negatively with negative symptoms in EOS patients, indicating a relationship between severity of the illness and reduced VMHC. Previous studies have consistently found that reduced volume in the STC is significantly correlated with clinical symptoms (Lui et al., 2009; Menon et al., 1995; Tang et al., 2012). Functional neuroimaging studies have also found significant correlations between STC activation and symptomatology in schizophrenia patents during language processing (Kircher et al., 2001; Plaze et al., 2006). Guo et al. (2014c) found similar results in adult schizophrenia; patients showed significant negative correlations between VMHC in STG and the PANSS negative and total scores. Interestingly, our recent study also observed a negative correlation between PANSS total score and VMHC in the PCG in adult chronic schizophrenia (Hoptman et al., 2012). The patients in the present study were younger and drug-naïve and thus extend our previous findings to include medication-free and young patients. This has important clinical significance and may suggest a role for VMHC in evaluating and predicting the severity of psychopathology.

There are several limitations to the present study. First, the sample size was relatively small, and a larger sample would increase the power of the study and the generalizability of the findings. Second, the present

study employed a cross-sectional design and is thus not able to separate intra- and intersubject variability. A follow-up design could provide longitudinal data to clarify the abnormal developmental changes of functional homotopy in EOS. On the other hand, the EOS patients had to be treated for ethical reasons, and thus, we cannot exclude the effects of medication in a follow-up study. Third, although we tried to match the age and sex between EOS patients and TDCs, the age range was still a little different. Two of the TDCs were under 10 years old (7.5 and 8 years old, respectively), while only one EOS patient was under 10 years old (9 years old). During group analysis, we controlled the age to reduce the influence of the age range differences. Moreover, because the EOS patients were first-episode and drug-naïve, they might have difficulties performing neuropsychological tasks. We did not collect neuropsychological data, especially tasks that required interhemispheric transfer of information. Further exploration of these tasks could clarify whether decreased functional homotopy is reflected in abnormal behaviors. Socioeconomic status and IQ were also not collected, and thus we could not explore the associations between these factors and dysfunctional homotopy in EOS. Finally, we employed a voxel-wise method rather than a region-wise approach. Region-based approaches show advantages for exploring brain structure or anatomy in both the clinical and normal populations. These advantages partially originate from the fact that well-established knowledge of brain structure and anatomy has been used to create brain parcellation templates used in the ROI approach. However, it is not an obvious advantage for functional analyses because a well-established functional parcellation of the human brain is currently lacking. Rich differences in local functional homogeneity exist (Zang, Jiang, Lu, He, & Tian, 2004; Zuo et al., 2013). This fact makes it problematic to extract the regional mean time series by applying these structural parcellation templates (Jiang et al., 2014). Notably, due to these variabilities, large-scale regional approaches for functional connectomes only exhibited moderate test–retest reliability (Wang et al., 2011). To address above challenges, the voxel-wise method proposed in Zuo et al. (2010) takes the advantage of the original high-resolution of the fMRI data and defines the functional connectivity between the 'homotopic voxels', which are one voxel and its left–right geometrically symmetric voxel. VMHC shows high test–retest reliability (Zuo et al., 2010). The region-wise assessment on the homotopic changes will be an interesting topic once a functional parcellation of the human brain is well established in future.

In summary, the present study found that EOS patients showed substantial deficits of interhemispheric coordination, providing neurodevelopmental evidence for the disconnection theory of schizophrenia. Moreover, decreased VMHC in the STC/PCG correlated with clinical symptoms. These findings suggest that functional homotopy in neurodevelopmental processes may play an important role in the functional changes underlying schizophrenia.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Additional materials and methods, and the correlation results.

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Key points

- Few studies investigated the disconnection hypothesis in early-onset schizophrenia.
- This study explored the homotopic connectivity in first-episode drug-naïve early-onset schizophrenia.
- Early-onset schizophrenia patients exhibited global and regional homotopic connectivity reductions. Lower homotopic connectivity values were observed within superior temporal cortex and postcentral gyrus.
- The lower interhemispheric synchronization was correlated with higher levels of negative symptoms.
- The findings provide novel neurodevelopmental evidence for the disconnection hypothesis of schizophrenia.

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